In-Vitro Simulation of NBCA Embolization for Arteriovenous Malformation

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Summary

Embolization using n-butyl-cyanoacrylate (NBCA) for arteriovenous malformation (AVM) is now a daily practice over the world, but there exists no objective data that can be a basis for discussion or decision-making on the best concentration and injection rate of NBCA mixture. The purpose of this study was to obtain objective data on control and behavior of NBCA mixture with an in vitro simulation system of NBCA embolization for AVM.

A nidus model made of a one-ml syringe filled with small beads was connected to a pulsatile flow circuit. A microcatheter was introduced just before the nidus model. Endoluminal pressures proximal and distal to the nidus and flow volume through the nidus were measured. Digital subtraction angiography (DSA) was performed to calculate transit time of the contrast medium (CM) through the nidus. NBCA was injected at various rates with an autoinjector and transit time of NBCA through the nidus was calculated.

27 trials were completed. Transit time of CM through the nidus model is well correlated to flow volume per unit of time through the nidus model. Shorter the transit time, larger was the flow volume per unit of time. The correlation was statistically significant (P < .0001). Though statistical significance was not attained, transit time of NBCA mixture at 50% concentration had a tendency to be correlated to flow volume per unit of time through the nidus, and slower injection of the NBCA mixture led to slower filling of the nidus model.

Though this simulation system was artificial and the results should be interpreted carefully, it was shown with this system that transit time of CM through the nidus could be a good index for flow volume per unit of time through the nidus. Also suggested was a possibility to utilize this in vitro system for research and training on NBCA embolization of AVM.

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Introduction

Embolization using n-butyl-cyanoacrylate (NBCA) for arteriovenous malformation (AVM) is now a daily practice over the world. But its control or handling is learned only on clinical practice, and we have no objective indices to decide the concentration and injection rate of NBCA mixture in relation to the flow characteristics of the target of our therapy. Though in vitro simulation study cannot fully reproduce the clinical setting of NBCA embolization and its results should be carefully interpreted, it may be helpful in order to find some objective indices with which we can analyze our clinical experience and improve therapeutic decision-making.

In this study we tried to develop an in vitro system to simulate NBCA embolization of AVM, to evaluate some indices of flow dynamics of AVM, and to clarify relations among haemodynamic factors, operational factors, and behavior of NBCA.

Material and Methods

Pulsatile Flow Circuit:

Isoda's pulsatile flow circuit [1] was modified and applied to generate pulsatile flow (figure 1A). In brief explanation, this circuit consisted of two pumps; a constant flow pump and a pulsatile flow pump connected in parallel. The fluid running in this circuit was composed of; 2L of 10 times concentrated phosphate-buffered saline, 18L of non-ionized water, and 4L of low molecular weight dextran with a pH of 7.32-7.33 at its temperature of 21-25 degrees C.

Simulation Component

The simulation component comprised of an artificial nidus model connected via an extension tube and a Y-connector to the pulsatile flow circuit (figure 1B). The artificial nidus model was made by putting small beads (3.4 mm in radius or 2.5 x 4.5 mm in size) in a one-ml syringe (figure 1C). The proximal end of the artificial nidus was connected to an extension tube (3.2 mm in inner diameter and 50 cm long or 1.5 mm in inner diameter and 2 cm long) and then through one limb of a Y-connecter to the pulsatile flow circuit. Through the other limb of the Y-connecter, a microcatheter was inserted to the proximal end of the nidus model. The distal end of the nidus model is connected to a series of three extension tubes (3.2 mm in inner diameter and 50 cm long each) and the end of the last tube was then opened into a bucket.

Procedure

1. Monitor simultaneously endoluminal pressures just proximal to the nidus, through the microcatheter, and just distal to the nidus through a three-way cock.
2. Measure flow volume running through the nidus model by receiving the fluid pouring out from the distal end of the extension tube into the bucket, and calculate flow volume per unit of time (ml/min) through the nidus.
3. Run digital subtraction angiography (DSA) at 10 acquisitions/sec with contrast medium (CM) (300 mgI/100 ml) injected through the microcatheter at 0.3 ml/sec of injection rate with help of an autoinjector.
4. Replay the series of acquired images. Find the images where the top of CM just passed the proximal or distal end of the nidus model. Assume the time that elapsed between the two images as the transit time for the trial.
5. Under DSA, inject 1 ml of mixture of NBCA and Lipiodol at 80, 50, or 25% of NBCA concentration and push it with 5% glucose solution with an autoinjector at 2ml/min. Trials were additionally done with NBCA mixture at 50% concentration injected at 16, 4, and 1 ml/min of injection rate, as well as injected manually.
6. Replay the series of acquired images. Find the images where the top of NBCA mixture just passed the proximal or distal end of the nidus model. Assume the time that elapsed between the two images as the transit time for the trial.

Results

The full length of the procedure was accomplished in 27 trials: two trials with NBCA mixture at 25% concentration at 2 ml/min of injection rate, 11 trials with NBCA mixture at 50% concentration at 2 ml/min, 10 trials with NBCA mixture at 80% concentration at 2 ml/min, one trial with NBCA mixture at 50% concentration injected at each 16, 4, and 1 ml/min, one trial with NBCA mixture at 50% concentration injected manually.

Pressure waves monitored at the proximal and the distal to the nidus were pulsatile, but not physiological in the shape (figure 2). Mean pressure difference over the nidus model varied between 1-69 mmHg. Flow volume per unit of time through the nidus measured between 21.2-136.0 ml/min. Transit time of CM varied from 0.53 to 1.20 sec. NBCA mixture passed through the nidus model in 23 trials and transit time of the mixture varied from 0.40 to 40.14 sec. NBCA mixture did not pass the nidus model and occluded a proximal part of the nidus in 4 trials; two trials with NBCA mixture at 80% concentration of NBCA injected at 2 ml/min, one trial with NBCA mixture at 50% concentration at 2 ml/min, and one trial with NBCA mixture at 50% concentration injected manually.

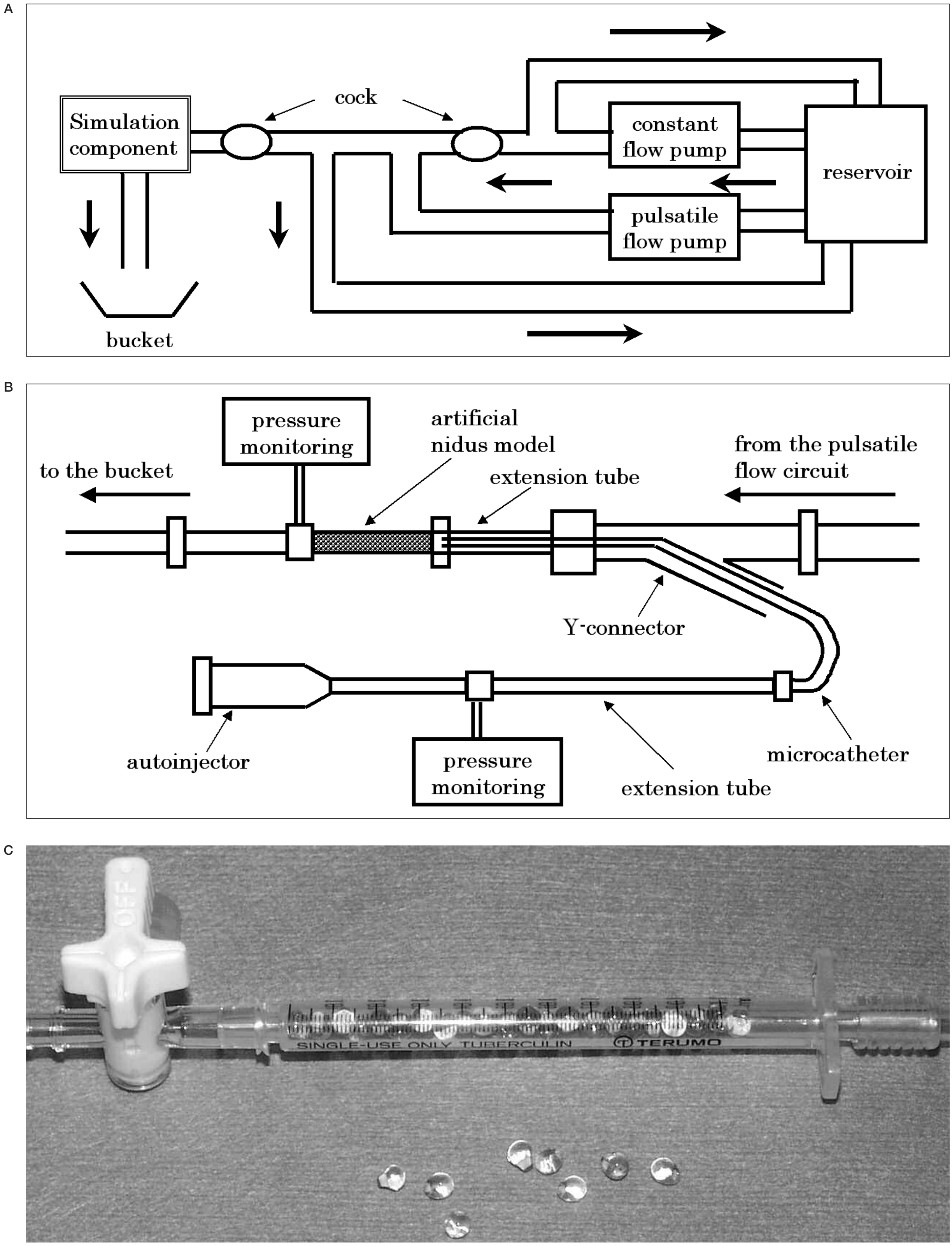

Figure 1 A) Diagram of the pulsatile flow circuit. B) Diagram of the simulation component with an artificial nidus model. C) An artificial nidus model made by putting small beads in a one-ml syringe.

Figure 2 Pressure waveforms: an example; A) pressure monitored just proximal to the nidus model, B) pressure monitored just distal to the nidus model. Pulsatile, biphasic change is observed, though not fully physiological in the form.

Mean pressure difference over the nidus model was not correlated to flow volume per unit of time through the nidus with statistical significance (P = .270278). Transit time of CM was well correlated to flow volume per unit of time through the nidus model (figure 3). Larger the flow volume per unit of time, shorter was the transit time. This correlation between transit time of CM and flow volume per unit of time was statistically significant (P = .000282).

Transit time of NBCA mixture at 50% concentration injected at 1, 2, 4, 16 ml/min of injection rate as well as injected manually is shown in the same figure (figure 4). When NBCA mixture at 50% concentration was injected at 2 ml/min of injection rate, transit time of the mixture showed a tendency to be correlated to flow volume per unit of time through the nidus model. But in one trial, NBCA mixture did not pass the nidus model and occluded a proximal part of it. This precluded statistical significance. The transit time for this trial is plotted as infinity in the figure.

When NBCA mixture at 50% concentration

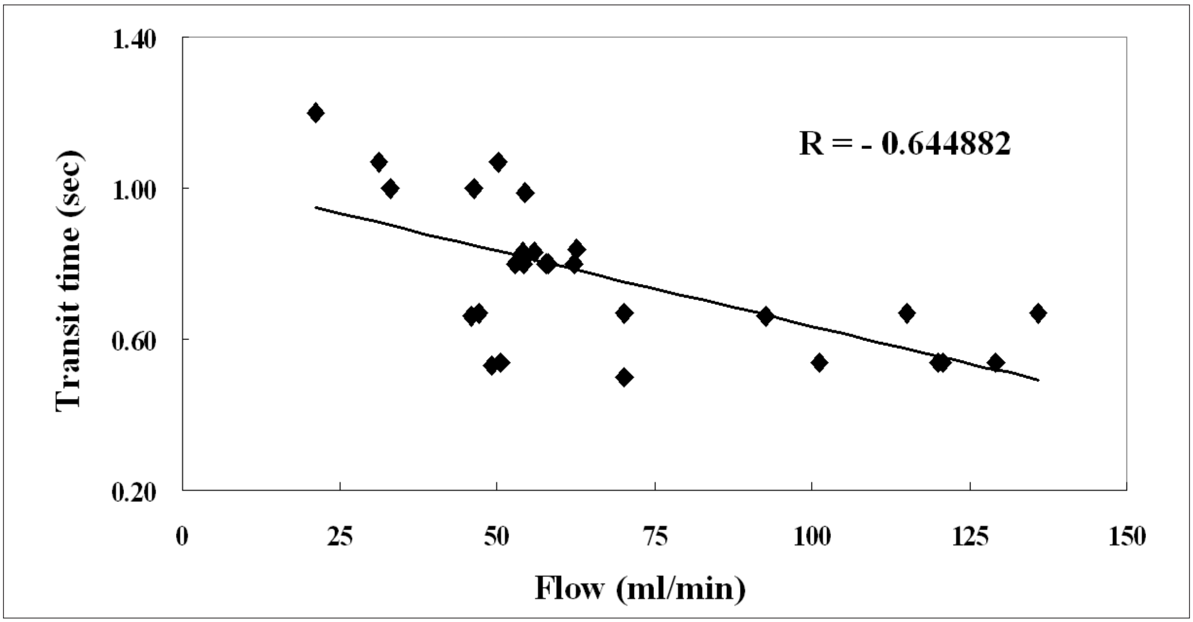

Figure 3 Transit time of contrast medium (CM) (sec) through the nidus model is plotted as a function of flow volume per unit of time (ml/min) through the nidus model. Transit time of CM is well correlated to flow volume per unit of time. Shorter the transit time, larger the flow volume per unit of time is. The correlation coefficient (r) is - 0.644882, and the coefficient of determination (R2) is 0.415872. The P value is 0.000282, which means that the correlation is statistically significant.

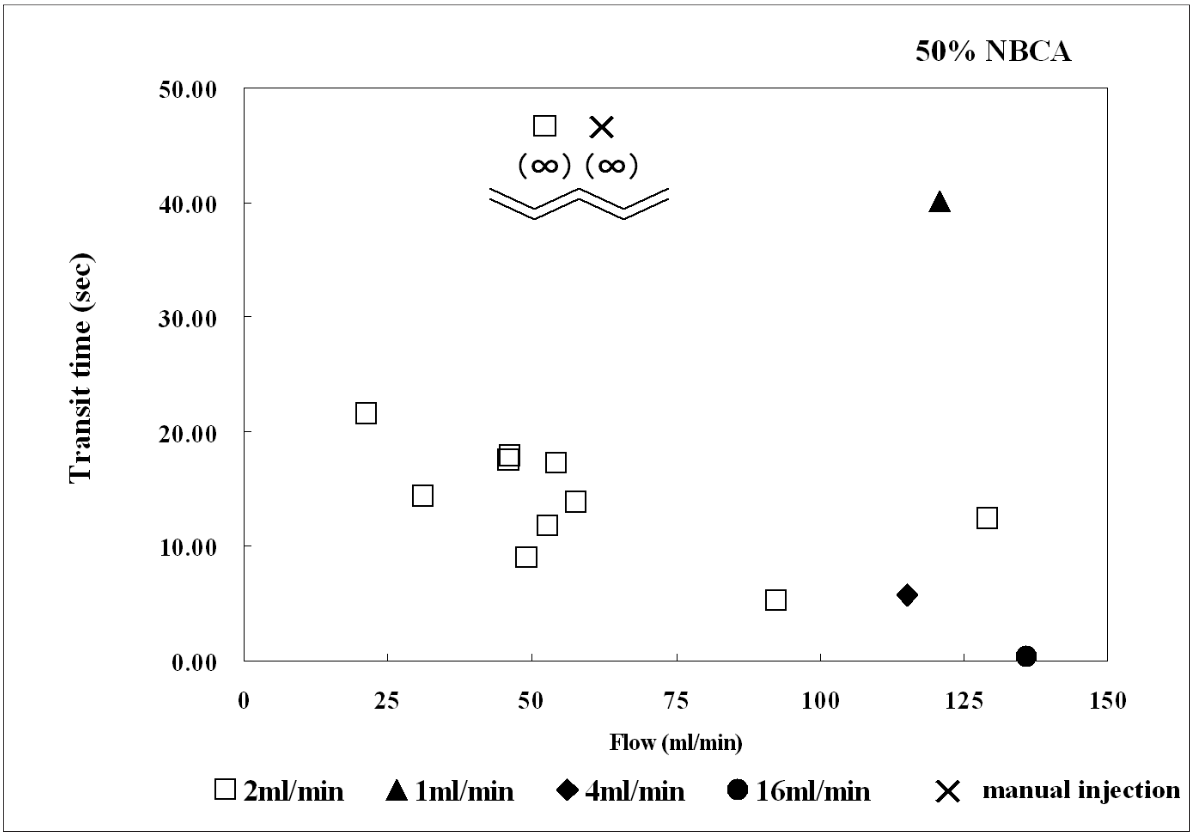

Figure 4 Transit time through the nidus model of NBCA at 50% concentration injected at 1, 2, 4, 16 ml/min and injected manually is plotted as a function of flow volume per unit of time (ml/min) through the nidus model. When NBCA mixture does not pass the nidus model, the transit time is plotted as infinity. When the mixture is injected at 2ml/min of injection rate, transit time of the mixture shows a tendency to be correlated to flow volume per unit of time through the nidus model, but no statistical significance is noted. Injected at 16, 4, 2, 1 ml/min in the flow through the nidus model around 120 ml/min, slower injection leads to slower filling of the nidus model. Injected manually, NBCA mixture slowly occluded proximal 70% of the nidus model and did not pass the nidus.

was injected at 16, 4, 2, 1 ml/min, in one trial for each injection rate, in the flow through the nidus model around 120 ml/min, slower injection led to slower filling of the nidus model (figure 4). When NBCA mixture at the same concentration was injected manually, it slowly occluded proximal 70% of the nidus model and did not pass the nidus.

Transit time of NBCA mixture at 25, 50, and 80% concentration injected at the same rate of 2 ml/min is shown in the same figure (figure 5). Transit time of 80% NBCA and that of 25% NBCA showed a tendency to be shorter than that of 50% NBCA. NBCA mixture at 50% concentration did not pass the nidus model in one trial as well as that at 80% concentration in two trials. In these cases where the mixture did not pass the nidus model, the transit time is plotted as infinity in the figure.

Discussion

In these years, embolization with NBCA for AVM is a therapy of choice undertaken all over the world. But its control or handling is learned only on clinical practice in days of our apprenticeship, and even later as a main operator, we have no objective indices when we are to decide the concentration and injection rate of NBCA mixture on the basis of the flow characteristics of the target of our therapeutic intervention, or to later discuss with others on the choice of the concentration and injection rate taken at the therapeutic session.

In vitro simulation of AVM embolization have been reported since late 1970's [2-7], but the purposes of these studies were mainly for teaching and training, and not for research, though possibility of application of these mod-

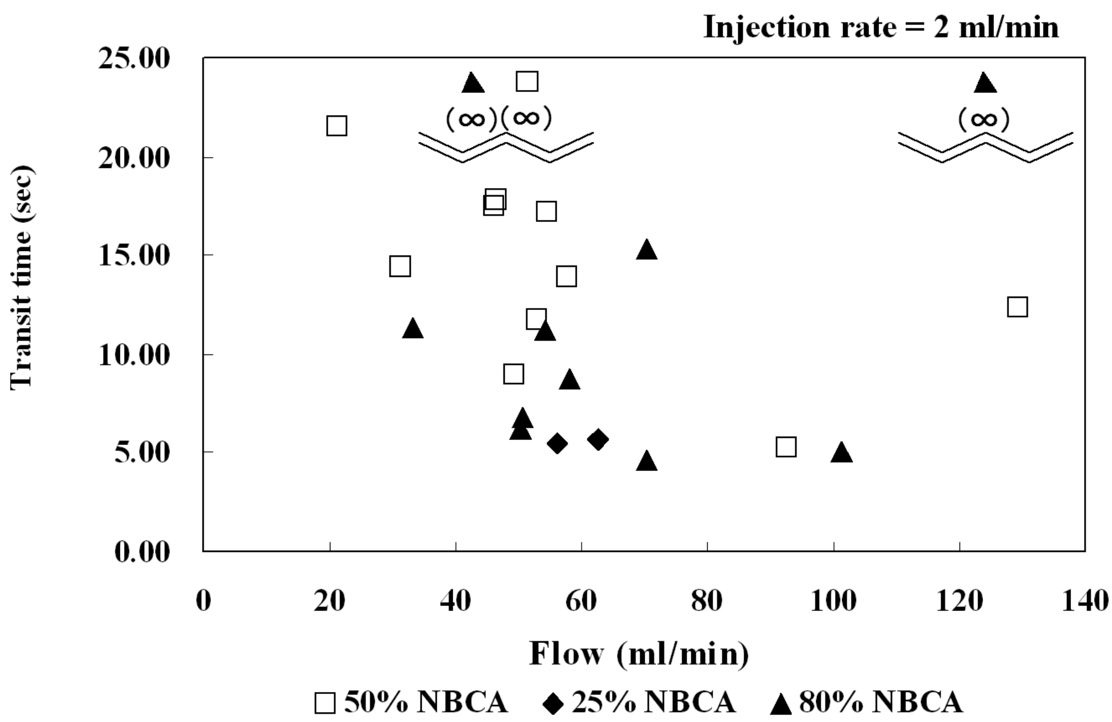

Figure 5 Transit time of NBCA mixture at 25, 50, and 80% concentration injected at the same rate of 2 ml/min is plotted as a function of flow volume per unit of time (ml/min) through the nidus model. Transit time of 80% NBCA and that of 25% NBCA showed a tendency to be shorter than that of 50% NBCA. NBCA mixture at 50% concentration did not pass the nidus model in one trial as well as that at 80% concentration in two trials, and the transit time in these trials is plotted as infinity in the figure.

els in research domain was mentioned in some of these reports. Another article[8] tackled on in vitro simulation of embolization to collect objective data including flow characteristics and results of embolization, but they used polyvinyl acetate as an embolization agent.

In our study, we focused our efforts on deriving some objective indices that can help us decide on the concentration and injection rate of NBCA mixture in a clinical setting. We made clear the relationship of transit time of CM through the artificial nidus and flow volume per unit of time through the nidus, and analyzed the influence of concentration and injection rate of NBCA mixture and flow volume per unit of time through the nidus upon transit time of NBCA mixture through the nidus. To our knowledge, this is the first report dealing with the relation between transit time of CM through an in vitro AVM nidus model and its flow characteristics as well as other relations among haemodynamic factors, operational factors, and results in in vitro simulation of NBCA embolization.

With materials available to us at this period of time, full reproduction of vascular structure of AVM is impossible. For example, endoluminal surface of an artificial tube is different from that of physiological vessels. Even though an interesting report[9] showed that materials of vessels, either vinyl or animal vein, made no difference in polymerization of NBCA mixture in vessels filled with still blood, straight extrapolation to the flowing fluid condition should not be made at the moment. Walls of vessels in living creatures are elastic, while tubing material available for in vitro simulation is rigid and non-elastic. Blood is not a Newtonian fluid, while fluid we usually use is Newtonian. These were some of the limitations in our in vitro simulation system. Even if we took elastic materials and non-Newtonian fluid, adjustment of elasticity, resistance of vessels, and characteristics of the non-Newtonian fluid to reproduce the real conditions in living beings would be of tremendous complexity, and make another field of study, the field of flow dynamics and biomechanics. Nevertheless, if we interpret the results of in vitro simulation study carefully with its limitations in our mind, it may be helpful in order to find some objective indices with which we can analyze our clinical experience and to improve therapeutic decision-making.

For the fluid running the circuit, we adjusted its pH to 7.32-7.33. Though it was still a little bit lower than in the normal arterial blood, it roughly reproduced the negatively charged condition of the normal blood, which is one of the prerequisites for polymerization of NBCA [10]. The temperature of the fluid was at the room temperature of 21-25 degrees C and may have made slower the polymerization time of NBCA than in the human blood [10,11]. These are other conditions to consider when we evaluate the results of this study. The range of the flow volume per unit of time through the nidus in this experiment was between 21.2-136.0 ml/min, and can be considered to represent low to at least moderate flow volume running into an AVM nidus from one of the feeding arteries, as the flow in feeding arteries at the level of the circle of Willis was reported to measure from 50 to 550 ml/min [12].

Mean pressure difference over the nidus model was not correlated to flow volume per unit of time through the nidus with statistical significance. One of the reasons could lie in the different ways of measuring pressure at the proximal and distal points to the nidus model, through a microcatheter at the former and through a three-way cock at the latter. Diameter of the inner lumen of the three-way cock was smaller at the point just below the third arm of the cock than the other parts proximal or distal to this point, which could also influence the pressure measured at this point in the flowing fluid condition.

We assumed as transit time of CM or NBCA mixture the time that it took for the top of CM or NBCA mixture to pass the full length of the nidus model. This is a simpler way of measuring transit time than computer-assisted calculation based on the time-density curve of CM or NBCA mixture, and can be employed more easily at daily clinical practice.

Transit time of CM was well correlated to the flow volume per unit of time through the nidus model (figure 3) with statistical significance (P = .000282). Shorter the transit time, larger was the flow volume per unit of time. This result suggests that using transit time of CM as an index of flow per unit of time through a nidus in a clinical setting is on a significant scientific basis, even though this is derived from an in vitro simulation with some of the limits described above.

Transit time of NBCA mixture at 50% concentration injected at 2 ml/min of injection rate showed a tendency to be correlated to flow volume per unit of time through the nidus model (figure 4), though this tendency is not statistically significant. In one trial, NBCA mixture did not pass the nidus model and occluded only a proximal part of it, which may suggest existence of uncontrolled elements in the study setting. When NBCA mixture at 50% concentration was injected at 16, 4, 2, 1 ml/min, slower injection led to slower filling of the nidus model, and injection was well controlled manually to achieve a good obliteration of the proximal 70% of the nidus model. Though only one trial was done for each injection rate, this result corresponded well to our experience of daily practice.

Transit time of NBCA mixture at 25, 50, and 80% concentration injected at the same rate of 2 ml/min was not well correlated to the concentration of the mixture (figure 5). This can also suggest uncontrolled elements in the study setting. Or it may reveal another possibility that higher concentration of NBCA mixture does not necessarily lead to shorter polymerization time in some condition of flow rate and injection rate, where anions necessary for polymerization can not be recruited from the surrounding flowing fluid so much as higher concentration of NBCA in the mixture, as the contact surface of the NBCA mixture with the surrounding flowing fluid is rather constant among different concentrations of NBCA.

Conclusions

An in vitro system to simulate NBCA embolization of AVM was developed. Though this simulation system was artificial and the results should be interpreted carefully, it was shown with this system that transit time of CM through the nidus could be a good index for flow volume per unit of time through the nidus. Also suggested was a possibility to utilize this in vitro system for research and training on NBCA embolization of AVM.

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EDITORIAL COMMENT

This paper deals with a model of AVM that the authors potentially consider able to analyze the progression of NBCA according to the flow volume per unit of time through the nidus model. The model seems well built and the experiment well conducted; however the conclusions drawn by the authors have to be considered very cautiously. All the models that have been reported till now in the literature have never replaced properly in vivo experiences, and the model the authors have developed unfortunately does not fail to that rule. Summarizing an AVM to a syringe filled with beads, although potentially interesting, does not reflect the reality and does neither take in consideration the angioarchitecture of the lesion in which fistulas can be embedded necessitating thus the use of high concentration of glue, nor the haemodynamic equilibrium existing between the AVM and the surrounding brain ("the concept of host"). Furthermore, experience has proven that the deposition of glue varies according to various factors: type of lesion, architecture, type and size of the microcatheter, its position (wedged or free flow), velocity of injection, type of syringe used, concentration of glue etc... We all know that very often the injection speed has to be modulated during the glue deposition; therefore no precise recipe can be given at that stage concerning the optimal use of the acrylic embolus. Building up a model to understand the flow and the dynamics of blood or fluids is one thing that has its importance, taking its results as an "all way use" for daily practice is another challenge. The authors are fully right when they claim in their paper that "full reproduction of vascular structure of AVM is impossible". Embolization cannot be limited only to a model. As our therapeutic goal should be stabilization (eradication?) of the AVM in a given patient, the cast of glue has to be adapted to that same given patient according to the haemodynamic circumstances that the interventional neuroradiologist will have to face (the flow in an AVM changes if the patient is in apnea or in Valsalva during the glue injection).We have therefore to be cautious when we deal with the results of these in vitro experiments. We should resist the dogmas that they could easily carry (or the conclusions that we might too easily interpret as dogmas) as they will never replace in vivo personal experiences.

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